REMARKS

The examiner is invited to telephone the undersigned to discuss any issues deemed remaining after consideration of this amendment.

Submitted herewith is a Petition for a two months extension of time. The Petition authorizes a charge to our Deposit Account No. 19-0365 for the required fees for the extension of time. The grant of this extension makes January 7, 2004 the due date for response instead of November 7, 2002.

The Specification has been amended to recite Applicants' priority.

The claims have been amended to delete non-elected subject matter and to better define Applicants' invention.

Since the total number of claims do not exceed those already paid for, no fee is deemed due for the added Claims.

For ease of amendment Claims 1-31 have been cancelled without prejudice and new Claims 32 to 45 have been added.

Claim 32 is Claim 19 rewritten in independent form. In the rewritten Claim, the repetitive phrase "wherein R^{15} is as defined above" has been deleted.

Support for Claim 33 is found, for example, in original Claim 8.

Support for Claim 34 is found, for example, in original Claim 22.

Claim 35 is directed to the compounds of original Claim 2 (i.e., compounds of formula 1.0B), and Claim 35 incorporates the limitations of Claim 19.

Claim 36 is directed to specific compounds. Support for this Claim is found, for example, in Examples 118 to 132 on pages 159 to 163 of the above identified Application.

Support for Claims 37 to 45 is found, for example, in the Claims as originally filed and on pages 7 and 8 of the above identified Application.

Claims 32 to 45 are in the Application.

Applicants reserve the right to pursue the deleted subject matter in a continuing application.

Rejection: 35 U.S.C. §112, Second Paragraph

Claims 27-30 stand rejected under 35 U.S.C. §112, second paragraph for the reasons of record.

Applicants respectfully traverse this rejection.

Applicants' specification does conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which Applicants regard as the invention.

However, in order to expedite prosecution Applicants have amended the claims to recite the subject to whom the compound is administered.

The Examiner is requested to reconsider and withdraw this rejection.

Rejection: 35 U.S.C. §112, First Paragraph

Claims 1-18, 20-23, and 27-31 stand rejected under 35 U.S.C. §112, first paragraph for the reasons of record.

Applicants respectfully traverse this rejection.

Applicants' specification does contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and does set forth the best mode contemplated by the inventors of carrying out the invention.

On page 7 (line 3) to page 8 (line 24), for example, Applicants disclose the use of the claimed compounds. On page 340 to 341 Applicants disclose assays for assessing the activity of the claimed compounds. On pages 342 to 343 Applicants disclose the administration of the claimed compounds. The claimed compounds are described and methods of making the compounds are described.

However, in order to expedite prosecution, Claims 27 and 29 have been cancelled.

In Paragraph 4b (page 3 of the Office Action), the Office Action concludes that there is no nexus between inhibition of farnesyl protein transferase and (1) inhibition of abnormal growth of tumor cells wherein Ras protein is not activated; (2) inhibition of abnormal tumor cell growth wherein the ras oncogene is activated by a mechanism other than ras protein farnesylation; (3) inhibition of tumor cell growth wherein the Ras

protein is activated as a result of oncogenic mutation in genes other than the Ras oncogene; and (4) inhibition of nontumor abnormal cell growth.

Cancellation of Claims 27 and 29 to expedite prosecution renders the conclusions in Paragraph 4b moot.

Applicants' method claims are now directed to a method of treating certain cancers and to a method of inhibiting farnesyl protein transferase.

Applicants teach on page 7 at lines 11 to 12 that the compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. Applicants also teach on page 7 at line 33 to page 8 at lines 1-3 that this invention provides a method for inhibiting or treating the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of Applicants' compounds. Examples of tumors which may be inhibited are given in lines 3-12 on page 8.

No evidence or supporting authority has been cited to support the 35 U.S.C. § 112, first paragraph, rejection.

Khosravi-Far was published July 1992, and since that publication there have been other publications concerning the inhibition of farnesyl protein transferase and cancer.

Sepp-Lorenzino et al., Cancer Research 55, 5302-5309, November 15, 1995 was submitted in Applicants' parent Application. The Examiner is requested to notify the undersigned if another copy is desired. Sepp-Lorenzino et al. disclose the results of tests done with a peptidomimetic farnesyl protein transferase inhibitor (FTI). In the last sentence of the abstract the authors state:

> "We conclude that FPTase inhibitors are potent antitumor agents with activity against many types of human cancer cell lines, including those of wild-type ras."

In the Discussion section on page 5307, Sepp-Lorenzino et al. disclose that

> "The identification of activated gene products necessary for maintenance of the transformed phenotype raises the possibility of developing inhibitors of their activities as therapeutic agents. Ras is an attractive potential target because it is commonly activated in human cancer and

> because the biochemistry of its activation and the nature of its effects are at least partially understood. Moreover, since a specific set of posttranslational modifications of the Ras protein is required for the acquisition of biological activity, these reactions offer new targets for the development of specific inhibitors Thus, peptidomimetic inhibitors of FPTase, the first enzyme in the processing of Ras, were synthesized. We have tested one member of the family of FPTase inhibitors (FTIs) on a panel of human cell lines derived from a variety of malignancies. The data presented here demonstrate that the FTI is capable of inhibiting the anchorage-dependent and -independent growth of more than 70% of tumor cell lines tested...Together with the lack of toxicity to normal tissue, these data suggest that the FTIs could represent a new, potentially clinically useful class of agents."

See also the summary given in the first paragraph on page 5309.

Nagasu et al., Cancer Research 55, 5310-5314, November 15, 1995 was submitted in Applicants' parent Application. The Examiner is requested to notify the undersigned if another copy is desired. Nagasu et al. disclose the results of tests done with a farnesyl protein transferase inhibitor. In the last paragraph on page 5314 the authors state:

> "In summary, the data presented here confirm the hypothesis that, for ras-dependent tumors, inhibition of ras farnesylation results in inhibition of ras function and, therefore, inhibition of tumor growth. It seems plausible that a tumor might be ras dependent, even in the absence of the *ras* oncogene, thus broadening the spectrum of tumor targets for FTase inhibitors."

Kohl et al., Proc. Natl. Acad. Sci. USA, Vol. 91, pp.9141-9145, September 1994 was submitted in Applicants' parent Application. The Examiner is requested to notify the undersigned if another copy is desired. Kohl et al. disclose the results of

tests done with a farnesyl protein transferase inhibitor. In the last sentence of the paragraph bridging the first and second columns on page 9141 the authors state:

> "Here we demonstrate that a potent and selective small-molecule inhibitor of PFTase will inhibit the growth of *ras* -dependent tumors in animals at concentrations of compound that do not cause significant toxicity to host animals."

Kohl et al. state in the Discusion section on page 9144 that:

> "We have demonstrated that a synthetic, cell-active inhibitor of PFTase, L-739,749, can selectively inhibit the growth of *ras* -dependent tumors in a nude mouse explant model.
>
> ...
>
> It is likely that the antitumor effects of L-739,749 are due to its inhibition of PFTase activity.
>
> The current studies suggest that PFTase inhibitors such as L-739,749 will not only be effective antitumor drugs but may also prove to be remarkably safe chemotherapeutic agents."

Graham (Exp. Opin. Ther. Patents (1995) 5(12):1269-1285) was submitted in Applicants' parent Application. The Examiner is requested to notify the undersigned if another copy is desired. Graham discuses the uncertain role FT inhibitors may play in inhibiting tumor growth.

Graham, in the Conclusion section (pages 1280-1281), does state that:

> "However, there are several questions that remain to be answered before the clinical success of farnesylation inhibitors can be confidently predicted."

However, prior to that statement, Graham also states:

> "Although cell culture studies indicated that PFTase inhibitors would act primarily as cytostatic agents, the most recent *in vivo* studies involving H-ras transgenic mice demonstrate that tumor regression can be induced by inhibiting protein farnesylation."

Thus, Applicants believe that there is compliance with 35 U.S.C. §112 first paragraph.

The Examiner is requested to reconsider and withdraw this rejection.

Allowable Subject Matter

Claim 19 stands objected to as being dependent upon a rejected base claim. According to the Office Action, Claim 19 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants have rewritten Claim 19 as independent Claim 32.

Claim 19 depends on Claim 17, Claim 17 depends on Claim 16, Claim 16 depends on Claim 15, and Claim 15 depends on Claim 1.

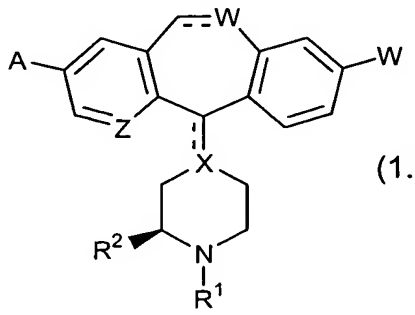
Claim 32 contains the limitations of Claims 1, 15, 16, 17 and 19.

The Examiner is therefore requested to reconsider and withdraw this objection.

Cited Documents

Applicants note the statements in the Office Action directed to U.S. 5,801,175 (Afonso et al.).

U.S. '175 discloses compounds of the formula:

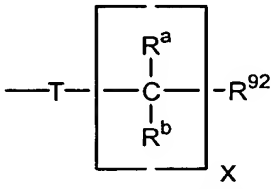


(1.0)

wherein R^2 can be, amongst others, a $-C(O)NR^6R^7$ substituent (see column 4 at about line 23). According to the disclosure in column 5 at about lines 20-25, R^6 and R^7 can optionally, together with the nitrogen to which they are bound, form a 5 to 7 membered heterocyloalkyl ring. According to the definition at column 7 at about lines

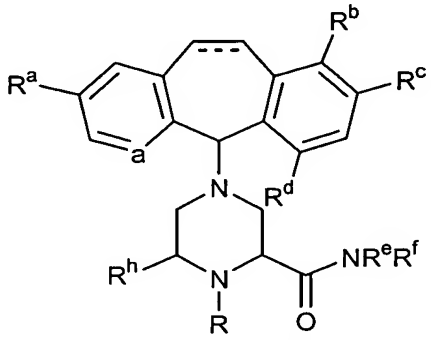
40-56, the definition of heterocycloalkyl includes piperidinyl and pyrrolidinyl. According to the definition, any of the available substitutable carbon and nitrogen atoms in the ring can optionally be substituted with one, two, three or more groups selected from C_1-C_6 alkyl, aryl, aralkyl, haloalkyl, amino, alkylamino, dialkylamino, -$S(O)_m$-aryl, -$C(O)R^9$ or an acyl radical of a naturally occuring amino acid.

R^1 can be, amongst others, a group of the formula:



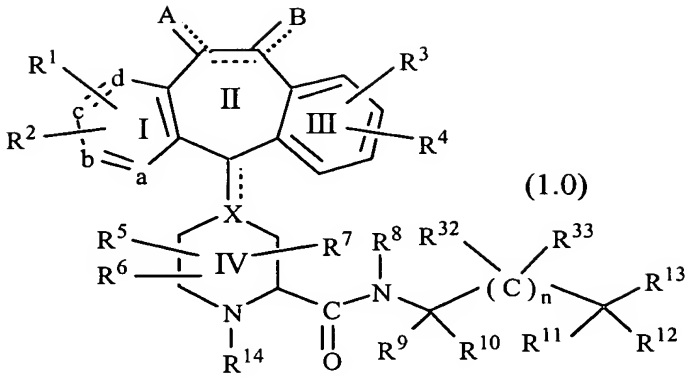
wherein T can be, amongst others, –C(O)-, -C(O)NH-, or –C(O)-O-; x can be, for example, 0 or 1; and R^{92} can be H, alkyl, aryl, aryloxy, arylthio, aralkoxy, aralkyl, heteroaryl or heterocycloalkyl.

Copending Application Serial No. 09/094,687 (our Docket No. IN0750K) filed June 15, 1998, priority to Provisional Application Serial No. 60/049,813 filed June 17, 1997, counterpart of WO98/57960 published December 23, 1998 (filed June 15, 1998 with priority to June 17, 1997) discloses compounds of the formula:



wherein R^e and R^f, amongst other possibilities, can be taken together with the nitrogen to which they are bound, to form a 5 or 6 membered heterocycloalkyl ring which can optionally be substituted. R^a to R^d can be selected from H or halo, amongst others. R can be, for example, -$C(O)R^1$ or –$C(O)NR^1R^2$.

Application Serial No. 09/465,553 filed December 16, 1999 (our Docket No. IN0973K1), priority to Provisional Application No. 60/113,141 filed December 18, 1998, issued as U.S. 6,372,747 on April 16, 2002 (pending divisional Application Serial No.10/026999 filed December 20, 2001) discloses compounds of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thererof, wherein:

one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c and d groups represent CR^1 or CR^2; or

each of a, b, c, and d are independently selected from CR^1 or CR^2;

X represents N or CH when the optional bond (represented by the dotted line) is absent, and represents C when the optional bond is present;

the dotted line between carbon atoms 5 and 6 represents an optional bond, such that when a double bond is present, A and B independently represent $-R^{15}$, halo, $-OR^{16}$, $-OCO_2R^{16}$ or $-OC(O)R^{15}$, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H_2, $-(OR^{16})_2$, H and halo, dihalo, alkyl and H, $(alkyl)_2$, -H and $-OC(O)R^{15}$, H and $-OR^{15}$, =O, aryl and H, $=NOR^{15}$ or $-O-(CH_2)_p-O-$ wherein p is 2, 3 or 4;

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{15}$, $-COR^{15}$, $-SR^{15}$, $-S(O)_tR^{16}$ (wherein t is 0, 1 or 2, $-N(R^{15})_2$, $-NO_2$, $-OC(O)R^{15}$, $-CO_2R^{15}$, $-OCO_2R^{16}$, -CN, $-NR^{15}COOR^{16}$, $-SR^{16}C(O)OR^{16}$, $-SR^{16}N(R^{17})_2$ (provided that R^{16} in $-SR^{16}N(R^{17})_2$ is not $-CH_2-$) wherein each R^{17} is independently selected from H or $-C(O)OR^{16}$, benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{15}$ or $-CO_2R^{15}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

R^5, R^6, and R^7 each independently represents H, $-CF_3$,

$-COR^{15}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{15}$, $-SR^{15}$, $-S(O)_tR^{16}$, $-NR^{15}COOR^{16}$, $-N(R^{15})_2$, $-NO_2$, $-COR^{15}$, $-OCOR^{15}$, $-OCO_2R^{16}$, $-CO_2R^{15}$, OPO_3R^{15}, or R^5 is combined with R^6 to represent =O or =S;

R^8 is selected from: H, C_3 to C_4 alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, substituted alkyl, substituted aryl, substituted arylalkyl, substituted heteroaryl, substituted heteroarylalkyl, substituted cycloalkyl, substituted cycloalkylalkyl;

the substutuents for the R^8 substituted groups being selected from: alkyl, aryl, arylalkyl, cycloalkyl, $-N(R^{18})_2$, $-OR^{18}$, cycloalkyalkyl, halo, CN, $-C(O)N(R^{18})_2$, $-SO_2N(R^{18})_2$ or $-CO_2R^{18}$; provided that the $-OR^{18}$ and $-N(R^{18})_2$ substituents are not bound to the carbon that is bound to the N of the $-C(O)NR^8-$ moiety;

each R^{18} is independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl or cycloalkyl;

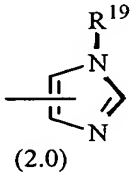
R^9 and R^{10} are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or $-CON(R^{18})_2$ (wherein R^{18} is as defined above); and the substitutable R^9 and R^{10} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^9 and R^{10} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring;

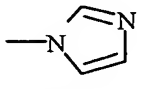
R^{11} and R^{12} are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, $-CON(R^{18})_2$ $-OR^{18}$ or $-N(R^{18})_2$; wherein R^{18} is as defined above; provided that the $-OR^{18}$ and $-N(R^{18})_2$ groups are not bound to a carbon atom that is adjacent to a nitrogen atom; and wherein said substitutable R^{11} and R^{12} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^{11} and R^{12} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring;

R^{13} is an imidazolyl ring selected from:

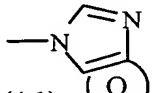


(2.0)



(4.0)

or

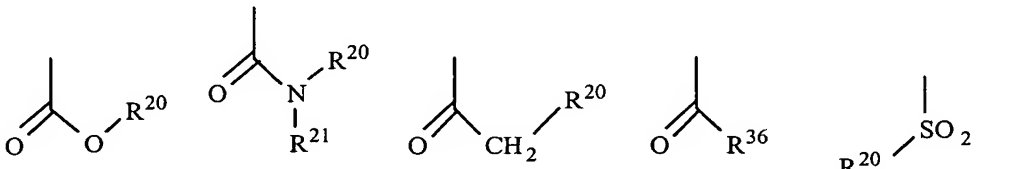


(4.1)

wherein R^{19} is selected from: (1) H, (2) alkyl, (3) alkyl, (4) aryl, (5) arylalkyl, (6) substituted arylalkyl wherein the substituents are selected from halo or CN, (7) -$C(aryl)_3$ or (8) cycloalkyl;

said imidazolyl ring 2.0 optionally being substituted with one or two substituents, and said imidazole ring 4.0 optionally being substituted with 1-3 substituents, and said imidazole ring 4.1 being optionally substituted with one substituent wherein said optional substituents for rings 2.0, 4.0 and 4.1 are independently selected from : -$NHC(O)R^{18}$, -$C(R^{34})_2OR^{35}$, -OR^{18}, -SR^{18}, F, Cl, Br, alkyl, aryl, arylalkyl, cycloalkyl, or -$N(R^{18})_2$ (wherein each R^{18} is independently selected); wherein R^{18} is as defined above; wherein each R^{34} is independently selected from H or alkyl; wherein R^{35} is selected from H, -$C(O)OR^{20}$, or -$C(O)NHR^{20}$, and R^{20} is as defined below; Q represents an aryl ring, a cycloalkyl ring or a heteroaryl ring, said Q is optionally substituted with 1 to 4 substituents inedependently selected from halo, alkyl, aryl, -OR^{18}, -$N(R^{18})_2$ (wherein each R^{18} is independently selected), -$OC(O)R^{18}$, or –$C(O)N(R^{18})_2$ (wherein each R^{18} is independently selected), and wherein R^{18} is as defined above;

R^{14} is selected from:



(5.0) , (6.0) , (7.0) , (7.1) or (8.0)

R^{15} is selected from: H, alkyl, aryl or arylalkyl;

R^{16} is selected from: alkyl or aryl;

R^{20} is selected from: H, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl, provided that R^{20} is not H when R^{14} is group 5.0 or 8.0;

when R^{20} is other than H, then said R^{20} group is optionally substituted with one or more substituents selected from: halo, alkyl, aryl, -$OC(O)R^{18}$, -OR^{18} or -$N(R^{18})_2$, wherein each R^{18} group is the same or different, and wherein R^{18} is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom;

R^{21} is selected from: H, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl or heterocycloalkyl;

when R^{21} is other than H, then said R^{21} group is optionally substituted with one or more substituents selected from: halo, alkyl, aryl, $-OR^{18}$ or $-N(R^{18})_2$, wherein each R^{18} group is the same or different, and wherein R^{18} is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom;

n is 0-5;

each R^{32} and R^{33} for each n are independently selected from: H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, $-CON(R^{18})_2$ $-OR^{18}$ or $=-N(R^{18})_2$; wherein R^{18} is as defined above; and wherein said substitutable R^{32} and R^{33} groups are optionally substituted with one or more substituents selected from: alkyl, cycloalkyl, arylalkyl, or heterarylalkyl; or

R^{32} and R^{33} together with the carbon atom to which they are bound, form a C_3 to C_6 cycloalkyl ring; and

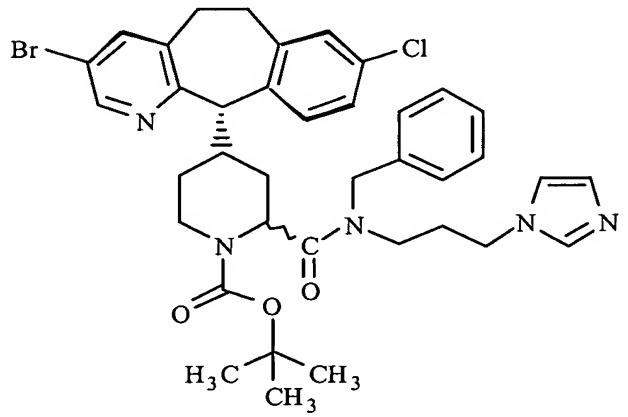
R^{36} is selected from branched alkyl, unbranched alkyl, cycloalkyl, heterocycloalkyl, or aryl; and

provided that:

(1) when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is N, then R^8 is selected from: C_3 to C_{10} alkyl, substituted C_3 to C_{10} alkyl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, cycloalkylalkyl, or substituted cycloalkylalkyl; and

(2) when R^{14} is selected from: group 6.0, 7.0, 7.1 or 8.0, and X is N, and R^8 is H, then the alkyl chain between R^{13} and the amide moiety is substituted.

Examples of such compounds include, but are not limited to:



(Example 78 Step B)

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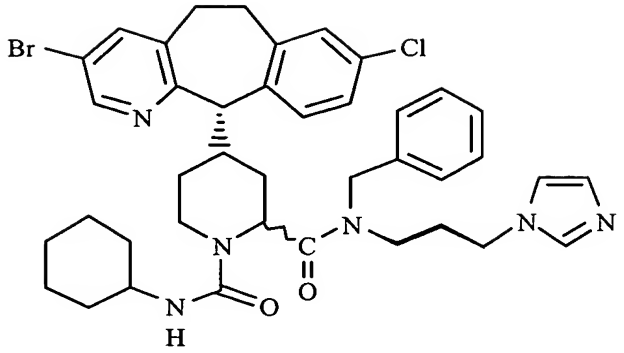

(Example 79 Isomer A)

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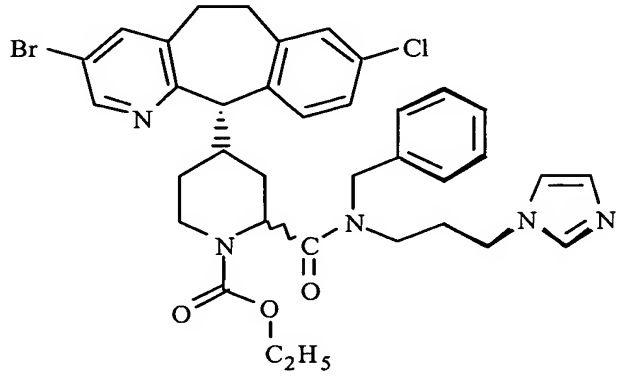

(Example 80 Isomer A)

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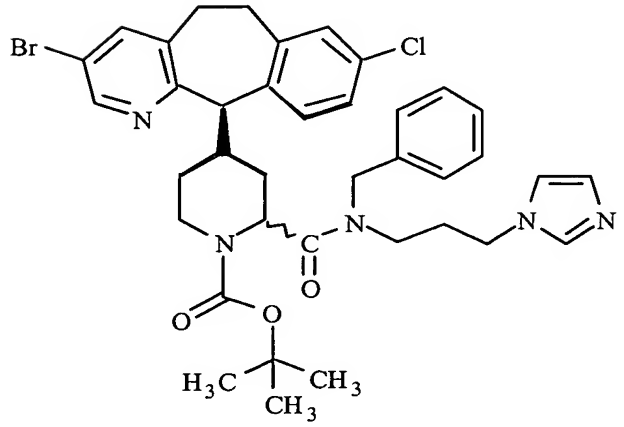

(Example 88 Isomer A)

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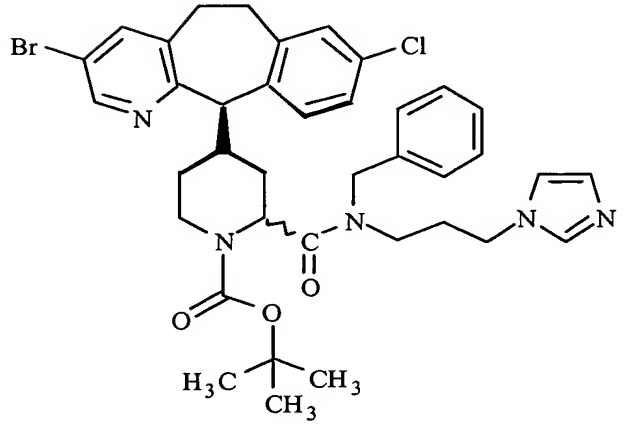

(Example 93 Isomer D)

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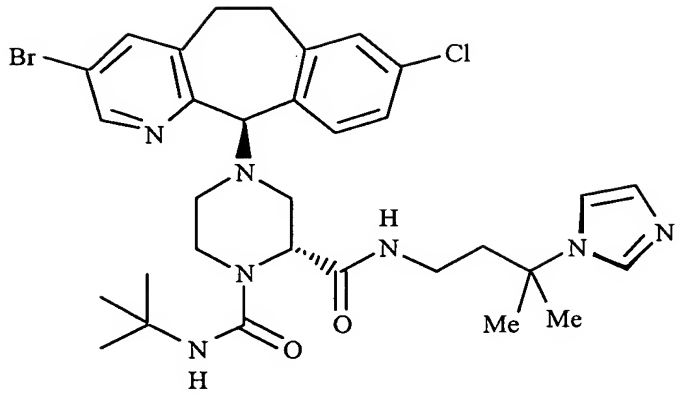

(11R,2R Isomer)

(Example 11)

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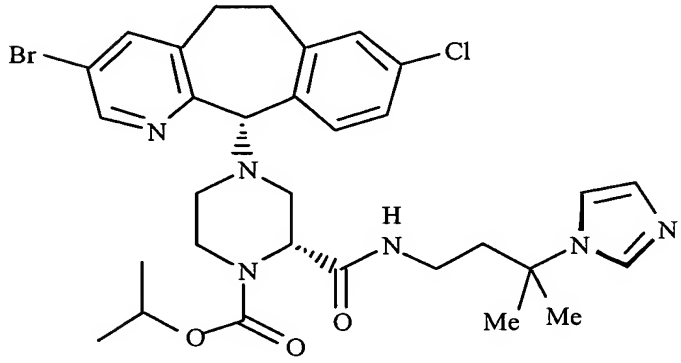

(11S,2R Isomer)

(Example 16)

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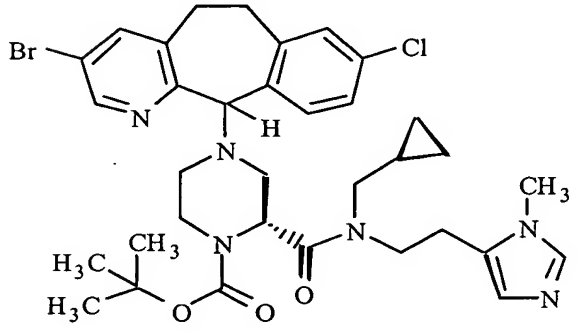
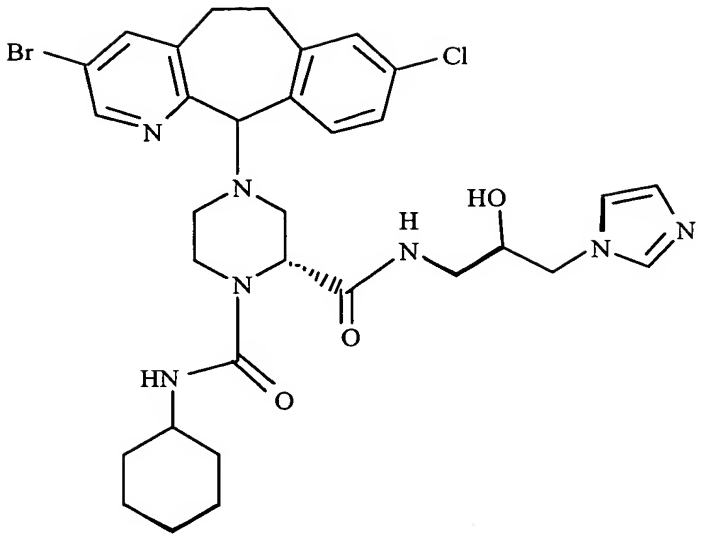


(Example 58) ;



(Example 99)

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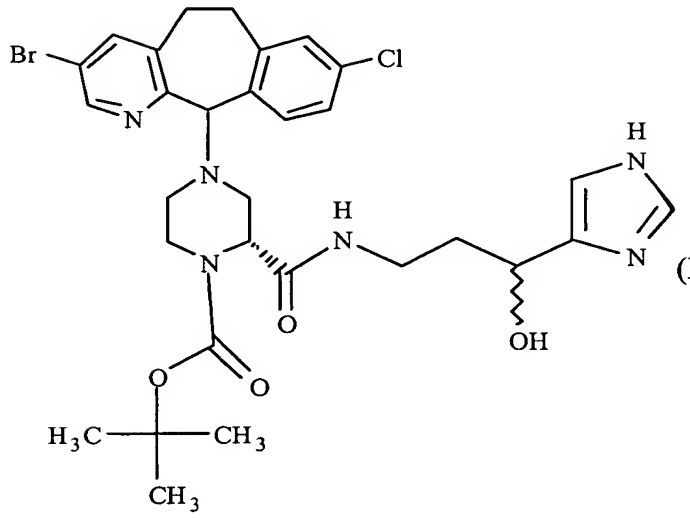

(Example 100)

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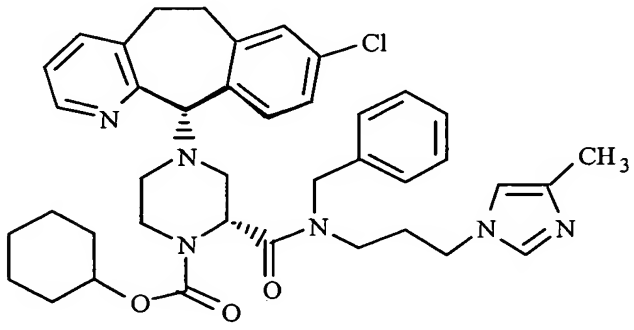

(Example 225)

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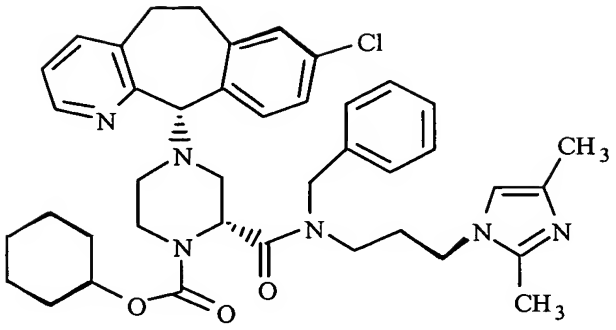

(Example 226)

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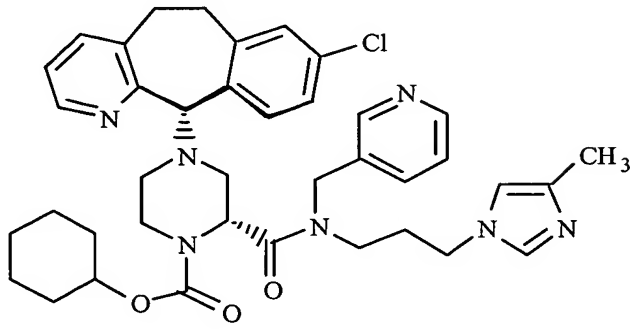

(Example 227)

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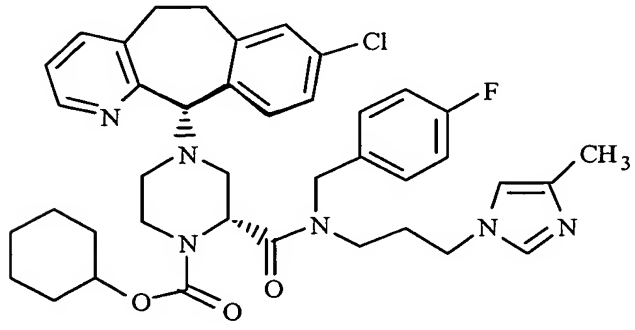

(Example 228)

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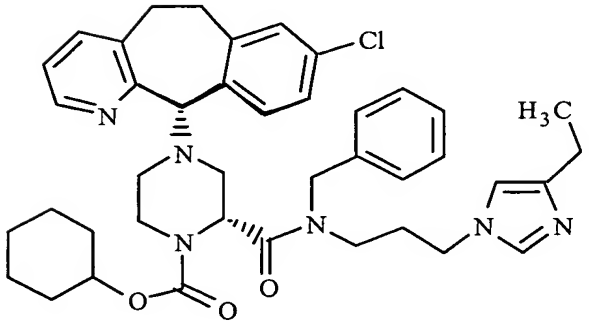

(Example 229)

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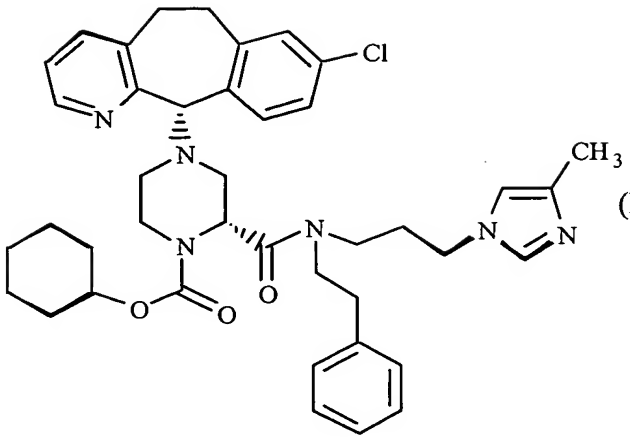

(Example 232)

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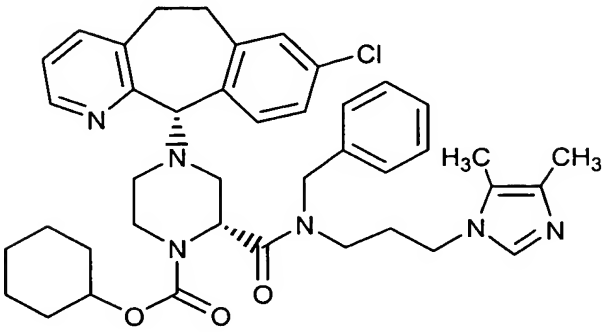

(Example 326)

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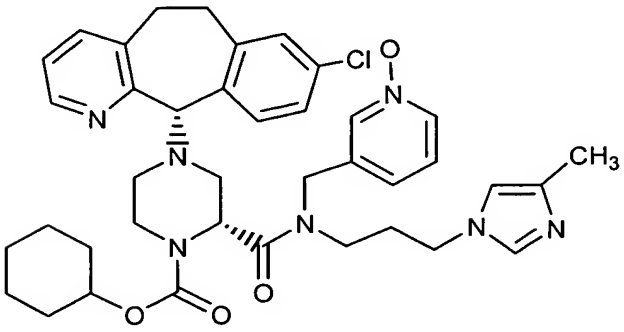

(Example 330)

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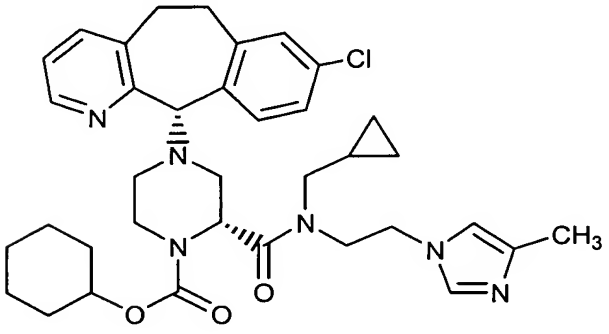

(Example 327)

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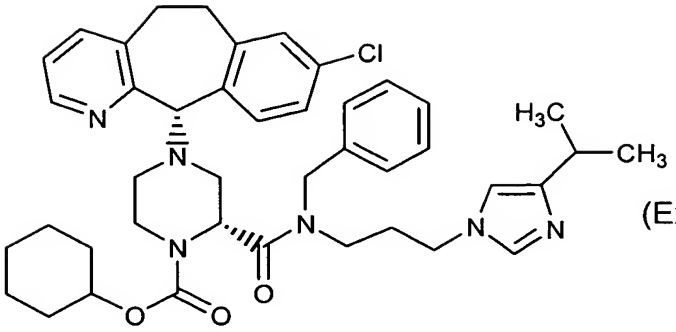

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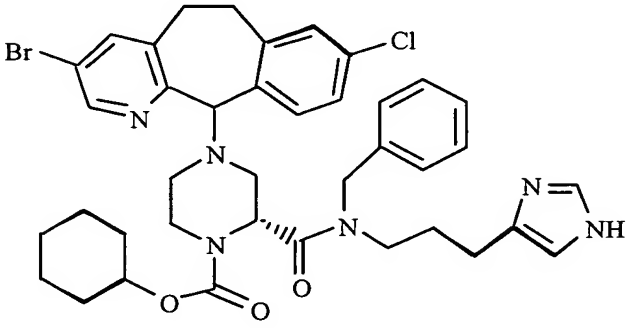

(Example 243)

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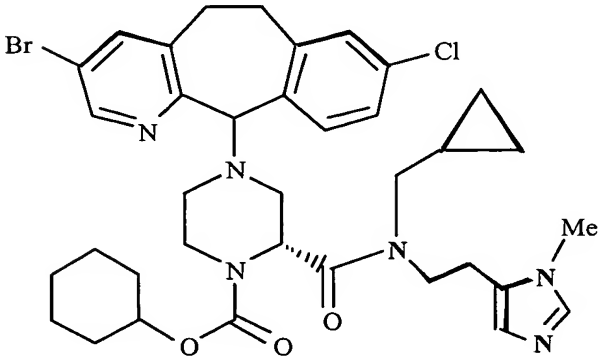

(Example 286A)

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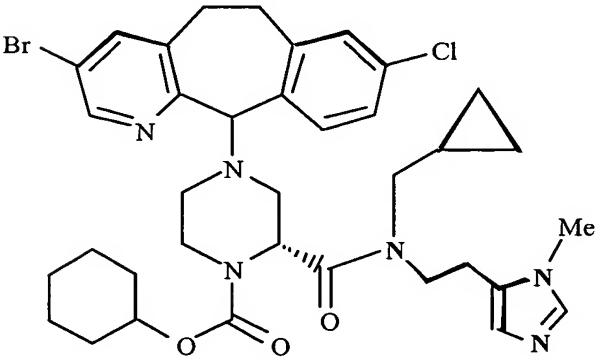

(Example 286B)

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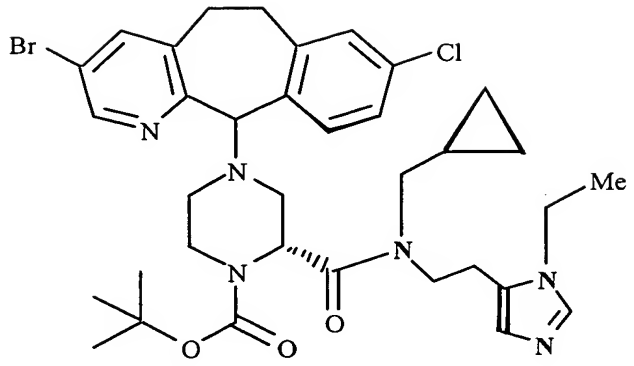

(Example 304)

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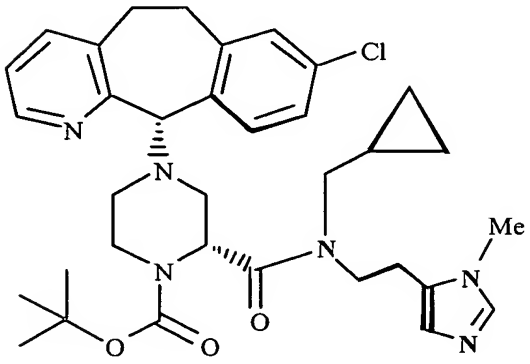

(Example 306)

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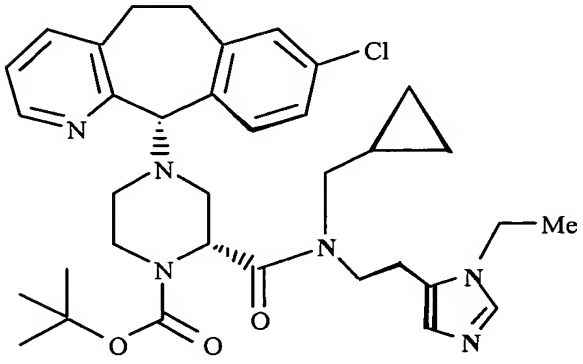
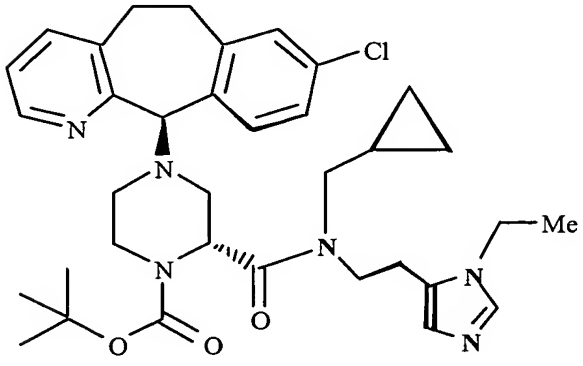


(Example 307)

; and



(Example 308)

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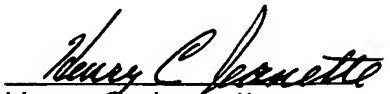
A copy of a Communication dated January 18, 2001 that was filed in Applicants' parent Application is enclosed herewith.

Respectfully submitted,



Henry C. Jeanette
Reg. No. 30, 856
Attorney for Applicants
(908) 298-5041